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Biotech Query for 09/610034

Title: **LIPOOLIGOSACCHARIDE BASED VACCINE FOR PREVENTION OF MORAXELLA (BRANHAMELLA)CATARRHALIS INFECTIONS IN HUMANS**

Inventor: **GU, XIN-XING**

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1: Vaccine. 2000 Nov 22;19(7-8):716-25. Related Articles, Links

Assessment of the stability and immunogenicity of meningococcal oligosaccharide C-CRM197 conjugate vaccines.

Ho MM, Bolgiano B, Corbel MJ.

Bacteriology Division, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, EN6 3QG, Hertfordshire, UK.

In this stability study, meningococcal C-CRM(197) conjugate vaccines from two different manufacturers that differ in oligosaccharide chain length, number of conjugation sites, conjugation chemistry, manufacturing process and formulation were used. Both the bulk concentrated and final fill preparations were incubated at -20, 4, 23, 37 or 55 degrees C for 5 weeks or subjected to ten cycles of freeze-thawing. The structural stability, hydrodynamic size and integrity of the treated vaccines were monitored by size exclusion chromatography (FPLC-SEC), high performance anion exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD) and fluorescence spectroscopy techniques. The data showed that the structural stability of the oligosaccharide chains and of the protein carrier varied between the two conjugates. The experimental immunogenicity was not severely affected by repeated freeze-thawing, incubation at -20 or 4 degrees C, but one developed conformational changes in the protein carrier when incubated at 23 degrees C or above, although the integrity of the oligosaccharide structure was maintained. This was not associated with any reduction in primary IgG or IgM antibody responses to meningococcal C polysaccharide. In the other conjugate vaccine, exposure to 55 degrees C resulted in the release of a substantial proportion of free saccharide that was accompanied by significant reduction in both IgG and IgM antibody responses to immunisation in the model system. In conclusion, the two meningococcal C-CRM(197) conjugate vaccines were stable when stored at the recommended temperatures, although their structural stability and subsequent immunogenicity were influenced by their conjugation chemistry and formulation.

PMID: 11115692 [PubMed - indexed for MEDLINE]

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Vaccine
Volume 19, Issues 7-8 , 22 November 2000, Pages 716-725

doi:10.1016/S0264-410X(00)00261-9 Cite or link using doi

Assessment of the stability and immunogenicity of meningococcal oligosaccharide C-CRM197 conjugate vaccines

Mei M. Ho, Barbara Bolgiano and Michael J. Corbel

Bacteriology Division, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Hertfordshire EN6 3QG, UK

Received 28 March 2000; revised 17 July 2000; accepted 1 August 2000. Available online 12 December 2000.

Abstract

In this stability study, meningococcal C-CRM_{197} conjugate vaccines from two different manufacturers that differ in oligosaccharide chain length, number of conjugation sites, conjugation chemistry, manufacturing process and formulation were used. Both the bulk concentrated and final fill preparations were incubated at -20, 4, 23, 37 or 55°C for 5 weeks or subjected to ten cycles of freeze-thawing. The structural stability, hydrodynamic size and integrity of the treated vaccines were monitored by size exclusion chromatography (FPLC-SEC), high performance anion exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD) and fluorescence spectroscopy techniques. The data showed that the structural stability of the oligosaccharide chains and of the protein carrier varied between the two conjugates. The experimental immunogenicity was not severely affected by repeated freeze-thawing, incubation at -20 or 4°C, but one developed conformational changes in the protein carrier when incubated at 23°C or above, although the integrity of the oligosaccharide structure was maintained. This was not associated with any reduction in primary IgG or IgM antibody responses to meningococcal C polysaccharide. In the other conjugate vaccine, exposure to 55°C resulted in the release of a substantial proportion of free saccharide that was accompanied by significant reduction in both IgG and IgM antibody responses to immunisation in the model system. In conclusion, the two meningococcal C-CRM_{197} conjugate vaccines were stable when stored at the recommended

temperatures, although their structural stability and subsequent immunogenicity were influenced by their conjugation chemistry and formulation.

Author Keywords: Meningococcal C-CRM197 conjugates; Stability; Physico-chemical analyses; FPLC; HPAEC-PAD; Immunogenicity

Corresponding author. Tel.: +44-1707-654753; fax: +44-1707-663796; email: mcorbel@nibsc.ac.uk

Vaccine
Volume 19, Issues 7-8 , 22 November 2000 , Pages 716-725

1: Infect Immun. 2003 Jul;71(7):4186-9. Related Articles, Links

Full text article at iai.asm.org

Antigen processing of the heptavalent pneumococcal conjugate vaccine carrier protein CRM(197) differs depending on the serotype of the attached polysaccharide.

Leonard EG, Canaday DH, Harding CV, Schreiber JR.

Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio 44106, USA.

The pneumococcal (Pn) conjugate vaccine includes seven different polysaccharides (PS) conjugated to CRM(197). Utilizing antigen-processing cells and a CRM(197)-specific mouse T-cell hybridoma, we found that the serotype of conjugated PnPS dramatically affected antigen processing of CRM(197). Unconjugated CRM(197) and serotype conjugates 14 and 18C were processed more efficiently.

PMID: 12819115 [PubMed - indexed for MEDLINE]

2: J Infect Dis. 2003 May 15;187(10):1629-38. Epub 2003 Apr 30. Related Articles, Links

The University of Chicago Press

Significant variation in serotype-specific immunogenicity of the seven-valent Streptococcus pneumoniae capsular polysaccharide-CRM197 conjugate vaccine occurs despite vigorous T cell help induced by the carrier protein.

Kamboj KK, Kirchner HL, Kimmel R, Greenspan NS, Schreiber JR.

Department of Pediatrics, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio 44106, USA.

Streptococcus pneumoniae capsular polysaccharides (PnPSs) induce protective antibodies but are T cell-independent type 2 antigens and are poorly immunogenic in infants. Conjugate vaccines of PnPSs linked to proteins like cross-reactive material (CRM(197)) increase PS antibody titer and elicit immunologic memory in infants. Despite being linked to an identical carrier protein, each PS component of the 7-valent PnPS-CRM(197) vaccine has different immunogenicity. To determine whether variations in conjugate-induced memory T cell responses or PnPS-specific antibody-secreting cells (ASCs) were responsible for serotype-specific differences in immunogenicity, adults were immunized with 7-valent PnPS-CRM(197), and antibody titer, vaccine component-specific CD4(+) T cell recall response, numbers of PnPS-specific ASCs, and cytokine production were measured. PnPS-CRM(197) induced significantly different serotype-specific antibody titers, despite vigorous T cell recall responses to all 7 vaccine components, and production of interleukin (IL)-2, IL-5, IL-6, IL-10, and interferon-gamma. We conclude that PnPS-CRM(197) induces variable serotype-specific antibody titers, despite induction of comparable CRM(197)-specific memory T cell responses.

Publication Types:
- Clinical Trial

PMID: 12721943 [PubMed - indexed for MEDLINE]

☐ 3: Vaccine. 2002 Nov 1;20(31-32):3658-67. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Effect of monophosphoryl lipid A (MPL) on T-helper cells when administered as an adjuvant with pneumococcal-CRM197 conjugate vaccine in healthy toddlers.

Vernacchio L, Bernstein H, Pelton S, Allen C, MacDonald K, Dunn J, Duncan DD, Tsao G, LaPosta V, Eldridge J, Laussucq S, Ambrosino DM, Molrine DC.

Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA. lvernacchio@slone.bu.edu

As new vaccines are developed, novel adjuvants may play an important role in eliciting an effective immune response. We evaluated the safety and adjuvant properties of monophosphoryl lipid A (MPL in 129 healthy toddlers immunized with two doses of nine-valent pneumococcal-CRM(197) protein conjugate vaccine (PCV9) combined with 10, 25, or 50 micro g of MPL with or without alum (AlPO(4)). Vaccine-specific humoral and cell-mediated responses were examined

following the second dose of study vaccine. All doses of MPL were well-tolerated and a dose-dependent effect of MPL on specific cellular responses was observed. The 10 micro g MPL dose significantly enhanced CRM(197)-specific T-cell proliferation (P=0.02) and interferon-gamma (INF-gamma) production (P=0.009) compared to responses of controls who received PCV9 with AlPO(4). In contrast, CRM(197)-specific T-cell proliferation and interferon-gamma production of the 50 micro g MPL/AlPO(4) group were decreased when compared to controls although these differences did not reach statistical significance. IL-5 and IL-13 responses after immunization showed a similar pattern with increased production in the 10 micro g MPL group and decreased production in the 50 micro g MPL/AlPO(4) group compared to controls. There were no differences in serum IgG antibody concentrations to the nine vaccine pneumococcal capsular polysaccharides and carrier protein between the MPL-containing and control vaccine groups. These findings demonstrate a dose-dependent effect of MPL on T-helper cell type 1 (TH-1) responses to the carrier protein and also suggest an effect on T-helper cell type 2 (TH-2) responses.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 12399193 [PubMed - indexed for MEDLINE]

☐ **4:** Infect Immun. 2002 Sep;70(9):5107-14. Related Articles, Links

Full text article at iai.asm.org

Immunogenicity in a mouse model of a conjugate vaccine made with a synthetic single repeating unit of type 14 pneumococcal polysaccharide coupled to CRM197.

Mawas F, Niggemann J, Jones C, Corbel MJ, Kamerling JP, Vliegenthart JF.

Division of Bacteriology, National Institute for Biological Standards and Control, South Mimms, Potters Bar, Herts EN6 3QG, United Kingdom. fmawas@nibsc.ac.uk

Oligosaccharides (OSs) related to the pneumococcal type 14 capsular polysaccharide (Pn14PS) were studied for their ability to inhibit the binding between anti-PS14 antisera and native PS14. A synthetic tetrasaccharide corresponding to the repeating unit of the Pn14PS, a hexasaccharide mimic, and an octasaccharide fragment obtained by Pn14PS depolymerization were good inhibitors. CRM197 conjugates of the tetrasaccharide and an octasaccharide mimic were prepared by using either adipic acid diester or diethyl squarate linkers. The conjugate with the tetrasaccharide chains

induced anti-Pn14PS antibodies when injected subcutaneously into mice, as determined by an enzyme-linked immunosorbent assay, and antibody titers increased with oligosaccharide loading. The adipic acid-linked tetrasaccharide conjugates elicited higher antibody titers than those prepared with a squarate spacer. The lower anti-Pn14PS antibody response of the octasaccharide mimic conjugate indicates the importance of the backbone galactose residue for an appropriate antibody response. The OS-CRM197 conjugate prepared from a single repeat unit of the Pn14PS is a potential vaccine candidate.

PMID: 12183560 [PubMed - indexed for MEDLINE]

☐ **5:** J Infect Dis. 2001 Oct 1;184(7):931-5. Epub 2001 Aug 22. Related Articles, Links

Immunization with Haemophilus influenzae type b-CRM(197) conjugate vaccine elicits a mixed Th1 and Th2 CD(4+) T cell cytokine response that correlates with the isotype of antipolysaccharide antibody.

Kamboj KK, King CL, Greenspan NS, Kirchner HL, Schreiber JR.

Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio, USA.

Haemophilus influenzae type b (Hib) capsular polysaccharide (PS) induces protective antibodies but is T independent and poorly immunogenic in infants. Conjugate vaccines of Hib PS linked to proteins, such as CRM(197), increase the PS antibody titer and elicit immunologic memory. To define the conjugate-induced memory T cell response, 19 adults were immunized with Hib-CRM(197), and antibody titers, carrier protein-specific CD4(+) T cell proliferation, and cytokine production were measured. Hib-CRM(197) induced PS and CRM(197) antibodies, vigorous T cell recall responses, and production of cytokines, including interleukin (IL)-2, IL-5, IL-10, and interferon-gamma. There was marked variability in PS antibody titer, despite consistent CRM(197)-specific recall responsiveness, which correlated with peak IgM and IgA PS antibody titers. Correlations were also found between IL-2 and IL-5 and IgA PS antibody levels. Hib-CRM(197) induced a rapid increase in CRM(197)-specific memory T cells and mixed Th1/Th2 cytokines, which may regulate the isotype and quantity of PS antibody.

PMID: 11528593 [PubMed - indexed for MEDLINE]

☐ **6:** Infect Immun. 2001 Jul;69(7):4698-701. Related Articles, Links

Synthetic polysaccharide type 3-related di-, tri-, and tetrasaccharide-CRM(197) conjugates induce protection against Streptococcus pneumoniae type 3 in mice.

Benaissa-Trouw B, Lefeber DJ, Kamerling JP, Vliegenthart JF, Kraaijeveld K, Snippe H.

Bijvoet Center, Department of Bio-Organic Chemistry, Utrecht University, Utrecht, The Netherlands. B.J.BenaissaTrouw@lab.azu.nl

Di-, tri-, and tetrasaccharides, synthesized according to the chemical structure of pneumococcal polysaccharide type 3 (PS3), were coupled to the cross-reactive material (CRM(197)) of modified diphtheria toxin in different molar carbohydrate/protein ratios using the squarate coupling method. To study protective immunity, female BALB/c mice were subcutaneously immunized twice (with a 3-week interval) using the amount of conjugates corresponding to 2.5 microg of oligosaccharide per mouse. The conjugates evoked PS3 binding immunoglobulin G antibodies that lasted for at least 7 weeks after the booster. Immunogenicity was not influenced by the carbohydrate/protein ratio. All mice with PS3-specific antibodies survived the intraperitoneal challenge with Streptococcus pneumoniae type 3. Therefore, synthetic oligosaccharide-protein conjugates might have potential as vaccines.

PMID: 11402020 [PubMed - indexed for MEDLINE]

☐ 7: Biotechnol Appl Biochem. 2001 Apr;33(Pt 2):91-8. Related Articles, Links

Biotechnology and Applied Biochemistry

Solution stability studies of the subunit components of meningococcal C oligosaccharide-CRM197 conjugate vaccines.

Ho MM, Lemercinier X, Bolgiano B, Crane D, Corbel MJ.

Division of Bacteriology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar EN6 3QG, U.K.

Spectroscopic methods were used to detect modifications in the structures of CRM197, the mutant diphtheria toxin, and meningococcal C capsular oligosaccharide following their conjugation and incubation at various temperatures. Meningococcal C oligosaccharide-CRM197 conjugate vaccines obtained from two different manufacturers were incubated at -20, 4, 23, 37 or 55 degrees C for 5 weeks or subjected to ten cycles of freeze-thawing. The CRM197 carrier protein and the saccharide components

of the treated vaccines were monitored by CD and NMR spectroscopic techniques. CD data indicated incubation temperature-dependent conformational changes in the carrier protein from vaccine A. Modifications appeared in both secondary and tertiary structures of the conjugated CRM(197) when incubated at 23 degrees C or above. This was characteristic of the 'open' conformation previously observed for this protein component. The NMR spectra also indicated modification of the structure of the conjugated CRM197 component of vaccine A when incubated at 23 degrees C or above, but failed to show any modification in the conjugated oligosaccharide. On the other hand, the structure of the oligosaccharide chains in vaccine B appeared to be degraded following incubation at 55 degrees C, even though the thermal effect on the conjugated CRM197 was less apparent. Repeated freeze-thawing did not affect the CD or NMR spectra. In conclusion, the two meningococcal C oligosaccharide-CRM197 conjugate vaccines were stable when stored at their recommended temperatures, but were differently affected by elevated temperatures. The conjugates differ in their conjugation chemistry, attachment positions, oligosaccharide chain length and loading, as well as recommended pH and storage buffer, and their different stability properties can probably be attributed to a combination of these factors.

PMID: 11277861 [PubMed - indexed for MEDLINE]

☐ **8:** Pediatr Infect Dis J. 2001 Feb;20(2):153-9. Related Articles, Links

Safety and immunogenicity of four doses of Neisseria meningitidis group C vaccine conjugated to CRM197 in United States infants.

Rennels MB, Edwards KM, Keyserling HL, Reisinger K, Blatter MM, Quataert SA, Madore DV, Chang I, Malinoski FJ, Hackell JG, Paradiso PR.

Center for Vaccine Development and Department of Pediatrics, University of Maryland School of Medicine, Baltimore, USA.

BACKGROUND: Following widespread use of conjugate pneumococcal vaccine, Neisseria meningitidis likely will become the leading cause of bacterial sepsis and meningitis in US children. This report describes the safety and immunogenicity in US children of four consecutive doses of a meningococcal group C vaccine conjugated to CRM197 via reductive amination (MnCC). METHODS: One hundred six healthy 2-month-old infants received MnCC at 2, 4 and 6 months of age in a randomized, controlled double blind study; children in the other treatment arm were given a 7-valent conjugate pneumococcal vaccine. Parents reenrolled 64 of these children at 12 to 15 months to receive a fourth dose of MnCC. Routine childhood vaccines, including DTP, were coadministered. Temperatures and

symptoms were recorded for 3 days after each immunization. Serum enzyme-linked immunosorbent assay IgG and bactericidal antibodies were measured prevaccination and before and 1 month after Doses 3 and 4. RESULTS: Moderate to severe local reactions, defined as erythema or induration > or =2.4 cm or pain that interfered with limb movement was reported after 0 to 3.2% of MnCC injections, depending on the reaction and dose. Fever occurred in 23 to 37% of children, but the contribution of MnCC to the febrile reactions is unknown. Geometric mean concentrations of IgG antibody to group C meningococcal polysaccharide were 3.72 microg/ml after Dose 3 and 8.03 microg/ml after the booster. Geometric mean functional serum bactericidal antibody titers after Doses 3 and 4 were 1:463 and 1:2341, respectively. One hundred percent of children had a serum bactericidal antibody titer of > or =1:64 after three doses and > or = 1:128 after the booster. CONCLUSIONS: The MnCC vaccine had an acceptable safety profile and generated high titers of bactericidal antibody in immunized US infants and toddlers. It appears to be an attractive candidate vaccine for the prevention of serogroup C meningococcal disease in young children.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 11224833 [PubMed - indexed for MEDLINE]

9: Dev Biol (Basel). 2000;103:93-104. Related Articles, Links

Characterization of saccharide-CRM197 conjugate vaccines.

Hsieh CL.

Wyeth-Lederle Vaccines, Sanford, North Carolina 27330, USA.

A seven-valent pneumococcal conjugate and a Group C Meningococcal conjugate are at the late stage of development. Clinical studies have demonstrated the efficacy and safety of these vaccines and licensure of these vaccines will be approved in the near future. Several new techniques have been proposed for characterizing polysaccharide-protein conjugates and their production intermediates. We are evaluating some of these new techniques, particularly NMR and MALLS, to determine whether or not they provide useful information for conjugate production. In the production of polysaccharide protein conjugates, the degree of saccharide activation, location of activation site, and the molecular weight of activated saccharides may typically be determined. In our evaluation, techniques such as NMR and MALLS may have a limited applicability for testing polysaccharides and activated saccharides.

Publication Types:

- Review
- Review, Tutorial

PMID: 11214258 [PubMed - indexed for MEDLINE]

10: Vaccine. 2000 Dec 8;19(9-10):1188-98. Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

A mucosal vaccine against diphtheria: formulation of cross reacting material (CRM(197)) of diphtheria toxin with chitosan enhances local and systemic antibody and Th2 responses following nasal delivery.

McNeela EA, O'Connor D, Jabbal-Gill I, Illum L, Davis SS, Pizza M, Peppoloni S, Rappuoli R, Mills KH.

Infection and Immunity Group, Department of Biology, National University of Ireland, Co. Kildare, Maynooth, Ireland.

The development of new generation vaccines against diphtheria is dependent on the identification of antigens and routes of immunization that are capable of stimulating immune responses similar to, or greater than, those obtained with the parenterally-delivered toxoid vaccine, while reducing the adverse effects that have been associated with the traditional vaccine. In this study, we examined the cellular and humoral immune responses in mice generated after both parenteral and mucosal immunizations with cross-reacting material (CRM(197)) of diphtheria toxin. We found that both native and mildly formaldehyde-treated CRM(197) and conventional diphtheria toxoid (DT) induced mixed Th1/Th2 responses and similar levels of anti-DT serum IgG following parenteral immunization. In contrast, CRM(197) preparations were poorly immunogenic when administered intranasally in solution. However, formulation of the antigens with chitosan significantly enhanced their immunogenicity, inducing high levels of antigen-specific IgG, secretory IgA, toxin-neutralizing antibodies and T cell responses, predominately of Th2 subtype. Furthermore, intranasal immunization with CRM(197) and chitosan induced protective antibodies against the toxin in a guinea pig passive challenge model. We also found that priming parenterally with DT in alum and boosting intranasally with CRM(197) was a very effective method of immunization in mice, capable of inducing high levels of anti-DT IgG and neutralizing antibodies in the serum and secretory IgA in the respiratory tract. Our findings suggest that boosting intranasally with CRM(197) antigen may be very effective in adolescents or adults who have previously been parenterally immunized with a conventional diphtheria toxoid vaccine.

PMID: 11137256 [PubMed - indexed for MEDLINE]

11: Vaccine. 2000 Dec 8;19(9-10):1159-66.

Serotype of Streptococcus pneumoniae capsular polysaccharide can modify the Th1/Th2 cytokine profile and IgG subclass response to pneumococal-CRM(197) conjugate vaccines in a murine model.

Mawas F, Feavers IM, Corbel MJ.

Division of Bacteriology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Hertfordshire EN6 3QG, Potters Bar, UK. fmawas@nibsc.ac.uk

The cellular and antibody responses to type 14 and type 19F Streptococcus pneumoniae capsular polysaccharides (PS) conjugated to CRM(197) were investigated in a mouse model developed for pre-clinical evaluation and quality control of pneumococcal conjugate vaccines. Total IgG antibody and IgG subclasses against PS and the carrier protein for both conjugates were measured in addition to the T cell proliferation and cytokine profiles induced by these conjugates. While unconjugated PS 14 and 19F were at best only weakly immunogenic, both types of conjugate induced strong primary and secondary IgG responses to PS. The responses induced by the two conjugates to the carrier protein were very different; a high level of anti-CRM(197) IgG was induced only by the PS19F conjugate whereas a very weak response was induced by the PS14 conjugate. Interestingly, the IgG subclass distribution was different for the two conjugates; for PS19F conjugate, the IgG response was almost completely of IgG1 subclass with low levels of IgG3 and IgG2a while the response to PS14 conjugate was mainly of the IgG1 and IgG2a subclasses with a low level of IgG3. The anti-CRM(197) IgG subclass distribution was identical with that to the corresponding conjugated PS. Both types of conjugate induced strong T cell proliferation to recall antigens but induced different patterns of cytokine response in immune spleen cells which were indicative of a Th0 response or a mixture of Th1 and Th2 responses with a bias towards Th2 response in PS19F-CRM(197) immunised mice. In conclusion, PS14- and PS19F-CRM(197) conjugates induced different IgG subclass patterns as a result of inducing different patterns of cytokine response to the carrier protein. This indicates that the serotype of PS can modify the Th1/Th2 response to the carrier protein, which has a direct effect and can predict the IgG subclass of the PS response. Finally, we conclude that this model appears suitable for studying the immunogenicity and immune interaction of different components of multivalent pneumococcal conjugate vaccines and may be applicable to their pre-clinical evaluation and quality control.

PMID: 11137252 [PubMed - indexed for MEDLINE]

☐ **12:** Vaccine. 2000 Nov 22;19(7-8):716-25. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Assessment of the stability and immunogenicity of meningococcal oligosaccharide C-CRM197 conjugate vaccines.

Ho MM, Bolgiano B, Corbel MJ.

Bacteriology Division, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, EN6 3QG, Hertfordshire, UK.

In this stability study, meningococcal C-CRM(197) conjugate vaccines from two different manufacturers that differ in oligosaccharide chain length, number of conjugation sites, conjugation chemistry, manufacturing process and formulation were used. Both the bulk concentrated and final fill preparations were incubated at -20, 4, 23, 37 or 55 degrees C for 5 weeks or subjected to ten cycles of freeze-thawing. The structural stability, hydrodynamic size and integrity of the treated vaccines were monitored by size exclusion chromatography (FPLC-SEC), high performance anion exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD) and fluorescence spectroscopy techniques. The data showed that the structural stability of the oligosaccharide chains and of the protein carrier varied between the two conjugates. The experimental immunogenicity was not severely affected by repeated freeze-thawing, incubation at -20 or 4 degrees C, but one developed conformational changes in the protein carrier when incubated at 23 degrees C or above, although the integrity of the oligosaccharide structure was maintained. This was not associated with any reduction in primary IgG or IgM antibody responses to meningococcal C polysaccharide. In the other conjugate vaccine, exposure to 55 degrees C resulted in the release of a substantial proportion of free saccharide that was accompanied by significant reduction in both IgG and IgM antibody responses to immunisation in the model system. In conclusion, the two meningococcal C-CRM(197) conjugate vaccines were stable when stored at the recommended temperatures, although their structural stability and subsequent immunogenicity were influenced by their conjugation chemistry and formulation.

PMID: 11115692 [PubMed - indexed for MEDLINE]

☐ **13:** J Urol. 2000 Oct;164(4):1329-33. Related Articles, Links

Comment in:

- J Urol. 2000 Oct;164(4):1334-5.

LWWonline LIPPINCOTT WILLIAMS & WILKINS

Inhibition of pressure induced bladder smooth muscle cell

hyperplasia using CRM197.

Haberstroh KM, Kaefer M, Bizios R.

Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, New York, USA.

PURPOSE: In vivo the effects of sustained hydrostatic pressure on the bladder wall and its components are evident under physiological and pathological conditions. We previously reported that exposure of bladder smooth muscle cells to 20 and 40 cm. H2O hydrostatic pressure for as little as 1 hour resulted in the up-regulation of heparin binding epidermal growth factor messenger RNA in a time dependent fashion as well as in activation of the heparin binding epidermal growth factor growth factor gene. In our current study we investigated the use of CRM197 as an agent for blocking undesirable cellular level events, such as smooth muscle cell hyperplasia, eliminating the irreversible alterations in bladder and kidney function that result from chronic and/or severe bladder outlet obstruction. MATERIALS AND METHODS: Control and experimental neonatal ovine smooth muscle cells were exposed to 0.3 pressure and 8.5 cm. H2O, respectively, for 7 days. We evaluated the mitogenic activity of the supernatant medium from bladder smooth muscle cells exposed to 8.5 cm. H2O for 5 days (conditioned medium) before and after the addition of 0.1 mg./ml. CRM197. Bladder smooth muscle cell apoptosis was also assessed after CRM197 exposure. Statistical analysis was performed using the Student t test with $p < 0.05$ considered significant. RESULTS: Exposing bladder smooth muscle cells to sustained 8.5 cm. H2O hydrostatic pressure for 7 days resulted in increased cell proliferation. Conditioned medium contained mitogenic activity, which was ablated after CRM197 was added. No direct toxic effect of CRM197 on bladder smooth muscle cell growth was appreciated (no apoptosis). CONCLUSIONS: We demonstrated a proliferative response of neonatal bladder smooth muscle cells after exposure to sustained hydrostatic pressure. This response was partially due to the release of heparin binding epidermal growth factor and was blocked by adding CRM197. These data support the potential use of CRM197 in drug targeted therapy for diseases involving bladder outlet obstruction.

PMID: 10992407 [PubMed - indexed for MEDLINE]

☐ **14:** Pediatr Infect Dis J. 2000 May;19(5):463-9. Related Articles, Links

Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants.

Obaro SK, Adegbola RA, Chang I, Banya WA, Jaffar S, Mcadam KW, Greenwood BM.

Medical Research Council Laboratories, Fajara, The Gambia.
sobaro@gamtel.gm

BACKGROUND: Unrelenting high morbidity and mortality have mandated that immunogenic vaccines be used to combat pneumococcal disease in infants. OBJECTIVES: To evaluate the safety and immunogenicity of a nonavalent pneumococcal conjugate vaccine and the antigenic interaction when administered simultaneously with diphtheria, tetanus and pertussis vaccines. METHODS: Two hundred seven infants were randomized to receive three doses of either nonavalent protein conjugate pneumococcal vaccine (PnCV) or inactivated polio vaccine (IPV) at 2, 3 and 4 months of age with routine Expanded Program of Immunization vaccines as scheduled. Vaccinees were visited on Days 1, 2 and 7 to observe local and systemic adverse reactions. Blood was drawn before the first dose and 1 month after the third dose. Antibody concentrations in sera were measured by standardized enzyme-linked immunosorbent assay. Nasopharyngeal carriage of pneumococci was tested at 5 and 9 months of age. RESULTS: No serious reactions were observed. Local induration and tenderness were observed more commonly at the site of administration of diphtheria, tetanus and pertussis vaccines than at the site of administration of IPV or PnCV. Between 79 and 91% achieved >1 microg/ml antibody against specific pneumococcal serotypes. Antibody responses to diphtheria and pertussis antigens were similar in both groups; however, antibody response to tetanus toxoid was significantly lower in infants who received PnCV (geometric mean concentration, 11.1 vs. 17.4; $P < 0.001$). Nasopharyngeal carriage in PnCV-vaccinated children was reduced but not significantly different from those vaccinated with IPV. CONCLUSION: Simultaneous administration of PnCV with Expanded Program of Immunization vaccines is safe and immunogenic. immune response to the composite antigens is likely to confer protection.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 10819345 [PubMed - indexed for MEDLINE]

☐ **15:** Pediatr Infect Dis J. 1999 Sep;18(9):757-63. Related Articles, Links

LWWonline
LIPPINCOTT WILLIAMS & WILKINS

Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers.

Shinefield HR, Black S, Ray P, Chang I, Lewis N, Fireman B, Hackell J, Paradiso PR, Siber G, Kohberger R, Madore DV, Malinowski FJ,

Kimura A, Le C, Landaw I, Aguilar J, Hansen J.

Kaiser Permanente Pediatric Vaccine Study Center of Northern California, Oakland, USA. henry.shinefield@kp.org

OBJECTIVES: The objectives of this study were (1) to determine the safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate (PNCRM7) vaccine in infants and (2) to determine the effect of concurrent hepatitis B immunization during the primary series and the effect of concurrent diphtheria and tetanus toxoid and acellular pertussis [DTaP (ACEL-IMUNE)] and conjugate CRM197 Haemophilus influenzae type b [HbOC (HibTITER) immunization at time of the booster dose on the safety and immunogenicity of PNCRM7and these other concurrently administered vaccines. METHODS: This was a randomized double-blinded study in 302 healthy infants in the Northern California Kaiser Permanente (NCKP) Health Plan. Infants received either PNCRM7 vaccine or meningococcal group C conjugate vaccine as a control at 2, 4 and 6 months of age and a booster at 12 to 15 months of age. Study design permitted the evaluation of immunology and safety of concurrent administration of routine vaccines. Antibody titers were determined on blood samples drawn before and 1 month after the primary series and the booster dose. RESULTS: After the third dose of PNCRM7 geometric mean concentrations (GMCs) ranged from 1.01 for serotype 9V to 3.72 microg/ml for serotype 14. More than 90% of all subjects had a post-third dose titer of > or =0.15 microg/ml for all serotypes, and the percentage of infants with a post-third dose titer of > or =1.0 microg/ml ranged from 51% for type 9V to 89% for type 14. After the PNCRM7 booster dose, the GMCs of all seven serotypes increased significantly over both post-Dose 3 and pre-Dose 4 antibody levels. In the primary series there were no significant differences in GMCs of pneumococcal antibodies between the subjects given PN-CRM7 alone or concurrently with hepatitis B vaccine. At the toddler dose concurrent administration of PNCRM7 and DTaP and HbOC resulted in a near conventional threshold for statistical significance of a post-Dose 4 GMC for serotype 23F [alone 6.75 mirog/ml vs. concurrent 4.11 microg/ml (P = 0.057)] as well as significantly lower antibody GMCs for H. influenza polyribosylribitol phosphate, diphtheria toxoid, pertussis toxin and filamentous hemagglutinin. For all antigens there were no differences between study groups in defined antibody titers that are considered protective. CONCLUSION: We conclude that PNCRM7 vaccine was safe and immunogenic. When this vaccine was administered concurrently at the booster dose with DTaP and HbOC vaccines, lower antibody titers were noted for some of the antigens when compared with the antibody response when PNCRM7 was given separately. Because the GMCs of the booster responses were all generally high and all subjects achieved similar percentages above predefined antibody titers, these differences are probably not clinically significant.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 10493334 [PubMed - indexed for MEDLINE]

☐ **16:** Infect Immun. 1999 Aug;67(8):4290-4. Related Articles, Links

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Expression and immunogenicity of a mutant diphtheria toxin molecule, CRM(197), and its fragments in Salmonella typhi vaccine strain CVD 908-htrA.

Orr N, Galen JE, Levine MM.

Department of Pediatrics, Division of Infectious Diseases and Tropical Pediatrics, Center for Vaccine Development, Department of Medicine, Division of Geographic Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.

Mutant diphtheria toxin molecule CRM(197) and fragments thereof were expressed in attenuated Salmonella typhi CVD 908-htrA, and the constructs were tested for their ability to induce serum antitoxin. Initially, expressed proteins were insoluble, and the constructs failed to induce neutralizing antitoxin. Soluble CRM(197) was expressed at low levels by utilizing the hemolysin A secretion system from Escherichia coli.

PMID: 10417208 [PubMed - indexed for MEDLINE]

☐ **17:** Clin Pediatr (Phila). 1998 Dec;37(12):760-1. Related Articles, Links

Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.

Steele RW.

Department of Pediatrics, Louisiana State University School of Medicine, New Orleans, USA.

PMID: 9864656 [PubMed - indexed for MEDLINE]

☐ **18:** Anal Biochem. 1998 Jun 15;260(1):24-9. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Quantitative restriction fragment length polymorphism: a

procedure for quantitation of diphtheria toxin gene CRM197 allele.

Pushnova EA, Zhu YS.

Chiron Corporation, Emeryville, California 94608-2916, USA.

Here we present an assay for quantitation of a particular gene allele in DNA mixtures by means of restriction fragment length polymorphism (RFLP) in combination with polymerase chain reaction (PCR). We applied the quantitative RFLP principle for estimation of the relative amount of diphtheria toxin gene CRM197 allele in Corynebacterium diphtheriae culture DNA samples. The procedure is based on PCR-mediated generation of an artificial AluI restriction site specifically with the CRM197 DNA template. After AluI digestion of the PCR product and polyacrylamide gel electrophoresis of the restriction fragments, the percentage of CRM197 template in the initial DNA sample was determined by scanning a gel negative. The method was shown to give a linear response when applied to template mixtures containing different amounts of CRM197 reference template. For samples where non-CRM197 DNA was detected by AluI RFLP, we designed a further allele-specific PCR assay to determine whether the non-CRM197 template portion was the wild-type toxin gene allele.

PMID: 9648648 [PubMed - indexed for MEDLINE]

19: J Infect Dis. 1982 Jan;145(1):94-102. Related Articles, Links

Diphtheria toxin and related proteins: effect of route of injection on toxicity and the determination of cytotoxicity for various cultured cells.

Pappenheimer AM Jr, Harper AA, Moynihan M, Brockes JP.

The effect of route of injection on the toxicity of intact diphtheria toxin, cross-reacting material (CRM45), and diphtherial fragment A was compared in several animal species. By ordinary routes of injection, neither CRM45 nor fragment A was toxic, even in species for which 0.1 micrograms of toxin/kg of body weight was lethal. After intracerebral injection, however, small amounts of CRM45 led to paralysis and death, even in mice and rats--species that are resistant to toxin administered intravenously. High doses of fragment A were nontoxic even by the intracerebral route. The cytotoxic dose od CRM45 was approximately 10(-7) M for a variety of cell lines derived from toxin-sensitive or toxin-resistant species. Cultured at Schwann's cells, however, were more sensitive CRM45 than other cell lines tested and 50-100 times more sensitive to toxin than cells cultured from other adult rat tissues. Fragment A has virtually no cytotoxicity for any mammalian cell line tested.

PMID: 6798133 [PubMed - indexed for MEDLINE]

☐ **20:** J Infect Dis. 1980 Nov;142(5):716-24. Related Articles, Links

Immunogenic correlation between cross-reacting material (CRM197) produced by a mutant of Corynebacterium diphtheriae and diphtheria toxoid.

Porro M, Saletti M, Nencioni L, Tagliaferri L, Marsili I.

The in vivo immunizing potency of diphtheria toxoid and formalin-treated corss-reacting material (CRM197, a nontoxic mutant protein) was compared in guinea pigs. Major antigenic differences between the two untreated proteins were also tested in rats. The results showed that diphtheria toxoid and CRM197 were equally effective immunogens, but only if the latter was treated with formalin in the same concentration (0.7% vol/vol) was that of the toxoid. Formalin treatment rendered the antigens more resistant to enzymatic proteolysis by trypsin in vitro.

PMID: 6780629 [PubMed - indexed for MEDLINE]

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#384 Phase I-II study of CRM197 administration to 50 advanced cancer patients.
Buzzi Silvio, Baccini Cesare, Rubboli Diego, Monti Giuseppe, Buzzi Giorgio, and Buzzi Anna Maria. *Centro Medico TRIS and Ospedale S.M. delle Croci, Ravenna, 48100, Italy.*

CRM197 is an immunogenic, nontoxic mutant of diphtheria toxin (DT). The molecule binds to both membrane anchored and secreted forms of heparin-binding epidermal growth factor (proHB-EGF and HB-EGF, respectively). ProHB-EGF is the specific cell receptor for DT and a juxtacrine mitogen with frequent overexpression in cancer. HB-EGF is an autocrine and paracrine mitogen and an adhesion factor. This study aimed to determine whether the binding of CRM197 to the growth factor inhibits its mitogenic effect and elicits an immune reaction affecting the tumor. CRM197 was injected s.c. in the abdominal wall of 50 advanced outpatients subdivided in three groups receiving 20, 40 or 60 Lf at a time for 6 times at 3 days' intervals. Main side effects were: mild inflammatory skin lesions, tolerable systemic reaction in hypersensitive patients, and hypotension. There were 3 complete responses (6%) lasting 88+, 80+, and 64 weeks, respectively. Partial response was achieved in 11 patients (22%) with a median duration of 8 weeks. A patient condition of cell-mediated hypersensitivity to DT/CRM197 and an increase in neutrophils, fibrinogen and C3c complement fraction after injection of the mutated toxin seemed to be predictive of a possible tumor response. At relapse, responders had no further improvement by a new systemic cycle. However, if CRM197 was administered by peritumoral injections to a s.c. lesion, the mass shrank again. We suggest that CRM197 can be given safely on an outpatient basis and that the molecule exerts antitumor activity.

Proceedings of the 1999 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.

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Immunity to Haemophilus influenzae type b polysaccharide capsule after vaccination with the complete series of oligosaccharide CRM197 conjugate vaccine in infants with human immunodeficiency virus infection.

J Pediatr. 1996 Mar;128(3):363-5. Unique Identifier : AIDSLINE MED/96370609

Peters VB; Sood SK; Department of Pediatrics, Mount Sinai School of Medicine, New; York, New York 10029, USA.

Abstract: We evaluated immunity to Haemophilus influenzae type b (Hib) in 18 human immunodeficiency virus-infected infants who were vaccinated with a complete series of Hib conjugate vaccine. Four months after the primary series, the geometric mean anticapsular antibody concentration in 11 children was 0.40 microgram/ml. There were no significant differences in CD4+ cell counts or in the Centers for Disease Control and Prevention disease classification according to the presence of immunity to Hib. Four months after the booster dose, the geometric mean anticapsular antibody concentration in the 18 children was 0.82 microgram/ml. Children with immunity were more likely than children lacking immunity to have higher CD4+ cell counts and mild human immunodeficiency virus-related disease. The majority of the anticapsular antibody concentrations were lower than in healthy children.

Keywords: Antibodies, Bacterial/*BLOOD *Bacterial Proteins/ADMINISTRATION & DOSAGE/IMMUNOLOGY CD4 Lymphocyte Count Haemophilus influenzae/*IMMUNOLOGY Haemophilus Infections/IMMUNOLOGY/*PREVENTION & CONTROL *Haemophilus Vaccines/ADMINISTRATION & DOSAGE/IMMUNOLOGY Human HIV Infections/COMPLICATIONS/*IMMUNOLOGY Immunization, Secondary Infant Prospective Studies Support, U.S. Gov't, P.H.S. *Vaccination *Vaccines, Synthetic/ADMINISTRATION & DOSAGE/IMMUNOLOGY JOURNAL ARTICLE

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